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A SINGLE ARM PHASE II STUDY OF HIGH-DOSE WEEKLY CARFILZOMIB PLUS  
CYCLOPHOSPHAMIDE AND DEXAMETHASONE IN THE TREATMENT OF RELAPSED  
MULTIPLE MYELOMA AFTER 1-3 PRIOR THERAPIES

Academic CRO Protocol Number: MYX.1  
Lead Group Protocol Number: MCRN-003

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to Amgen.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by the academic contract research organization (CRO)\* that is sponsoring the trial and Amgen to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Amgen and CRO. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Amgen and CRO of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CRO. The study may be terminated at any time by CRO or Amgen with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Amgen and CRO and must be kept in confidence in the same manner as the contents of this protocol.

\_\_\_\_\_  
Qualified Investigator  
(printed name and signature)

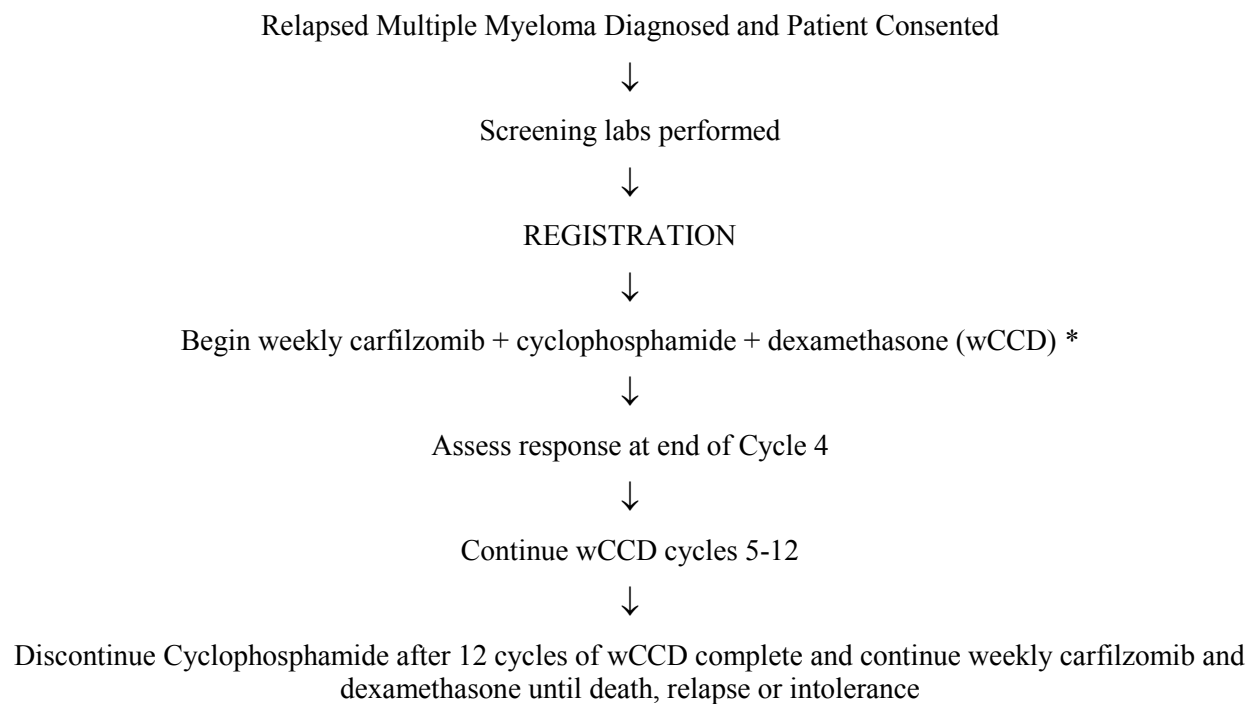
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Date

Protocol Number: MYX.1

CENTRE: \_\_\_\_\_

\* Canadian Cancer Trials Group (CCTG) acting as the academic contract research organization.

## TREATMENT SCHEMA



*\* there will be a 6 patient lead in phase where safety at 70 mg/m<sup>2</sup> will be evaluated in real time*

## 1.0 OBJECTIVES

This is a single arm phase II, investigator initiated, multicentre trial run through the Myeloma Canada Research Network.

### 1.1 Primary Endpoint

To determine the overall response rate after 4 cycles of weekly high-dose carfilzomib, cyclophosphamide and dexamethasone in patients with relapsed multiple myeloma after 1-3 prior regimens.

### 1.2 Secondary Endpoints

1.2.1 To determine the safety and toxicity profile of the combination.

1.2.2 To determine the depth of response including rates of stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) by current International Myeloma Working Group (IMWG) criteria.

1.2.3 To determine progression-free survival (PFS).

1.2.4 To determine the 2-year overall survival.

## 2.0 BACKGROUND INFORMATION AND RATIONALE

### 2.1 Multiple Myeloma

Multiple myeloma (MM) is an incurable lymphoproliferative disorder arising from clonal expansion of malignant plasma cells. It affects approximately 2000 Canadians annually [NCI Cancer Statistics 2013]. The clinical phenotype is characterized by the development of hypercalcemia, lytic bone disease, renal dysfunction (often due to light chain cast nephropathy, a product of the secreted clonal protein) and marrow suppression often resulting in anemia as well as other cytopenias. Treatment of the disease is focused on controlling the underlying clonal population to prevent further end-organ damage. Recent advances in management since the introduction of novel agents (NA) [Kumar 2008; Venner 2011] have resulted in long-term disease control measured in years. This is largely attributed to the increasing availability of effective treatment options at the time of relapse. Despite this the disease ultimately relapses. Moreover, due to inevitable clonal evolution and resistance to currently available therapies, the benefit of treatment diminishes with each subsequent line of therapy [Kumar 2004]. Double refractory patients have expected overall survival (OS) of less than 13 months [Kumar 2012a]. Thus, of particular importance is the development of regimens addressing patients previously exposed to NA such as proteasome inhibitors and immunomodulating agents; drugs now widely seen as standards in the therapy of this disease.

### 2.2 Proteasome Inhibitors in Myeloma

Bortezomib, the first in class proteasome inhibitor, is now widely used in the treatment of this disease. A number of bortezomib containing combinations have been explored in the treatment of patients with relapsed disease. Three drug combinations have become the standard, combining the proteasome inhibitor with dexamethasone and either an immunomodulation agent or an alkylator [Reeder 2014; Richardson 2010; San Miguel 2008; Stewart 2015]. Due to its ease of use and effectiveness Cyclophosphamide, Bortezomib, and Dexamethasone (CyBORd) has been widely adopted as a standard of care largely based on a small phase II trial [Reeder 2014]. This recent update from the initial publication in upfront patients demonstrated remarkable progression free survival (PFS) and OS. The dataset further described the impressive response rates showing the overall response for all patients (N=63) to be 89% with 62% achieving a very good partial response (VGPR) or better. Based on the recently published EVOLUTION trial this combination was also shown to be equivalent to lenalidomide, bortezomib, and dexamethasone (RVD), a potent regimen in both the upfront and relapsed setting, at substantially lower cost [Kumar 2012b]. Overall, this data supports the concept of a proteasome inhibitor in combination with the classic alkylator-steroid backbone as a potent standard treatment approach in the treatment of myeloma. In the relapsed setting triplet-based combinations remain an important therapeutic option. CyBORd has formally been evaluated by the Mayo Clinic in a series of 55 patients with progressive disease. The mean number of previous treatment lines was 3.3 and 36% and 82% were proteasome inhibitor and CyBORd naïve respectively. The overall response rate (ORR) was 71% with 26% achieving greater than VGPR and 13% a complete response (CR). In the proteasome naïve patients the overall response rate was 95% while in previously exposed patients it was 57% [Monge 2014]. In Canada, weekly dosing has become standard practice for the first-in-class proteasome inhibitor bortezomib, due to the documented preserved efficacy and the improved patient tolerability and convenience. Also, the combination of novel agents with oral weekly cyclophosphamide has been commonly utilized in Canada. The proposed study is designed to optimize the efficacy, tolerability, patient convenience and cost of a regimen based on carfilzomib, oral cyclophosphamide and dexamethasone by administering all agents on a weekly basis.

### 2.3 Carfilzomib in Myeloma

Given the potency of first-generation proteasome inhibitors the development of regimens including newer drugs in this class is being pursued with great interest. Carfilzomib has been examined as single agent and in combination with significant activity noted even in heavily pre-treated patients including those previously exposed to both proteasome inhibitors and immunomodulators. A triplet based regimen was explored in the ASPIRE trial which compared carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in relapsed patients after 1-3 prior regimens. The primary endpoint of the trial was progression free survival from the time of treatment initiation to disease progression or death. Patients were randomized to receive Carfilzomib 20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1 only, then 27 mg/m<sup>2</sup> on days 1,2, 8,9 and 15,16 of a 28-day cycle. A total of 792 patients were randomly assigned. Recently presented data demonstrates PFS was 26.3 months for the Carfilzomib arm versus 17.6 months with lenalidomide/dexamethasone alone [Stewart 2015].

While this result is encouraging recent evidence suggests that the optimal dose and schedule of carfilzomib has not yet been defined and higher doses could prove to be more effective in myeloma. Higher doses, given weekly along with dexamethasone, have been reported to be well tolerated and also effective. In a phase II trial using a dose of 56 mg/m<sup>2</sup> administered as a 30 minute infusion in relapsed and or refractory myeloma patients, 55% achieved a partial response or better [Lendvai 2014]. This compares favourably to a previous phase I result of 23% partial response (PR) or better using 20 mg/m<sup>2</sup> in cycle I followed by 27 mg/m<sup>2</sup> as a 10 minute infusion twice weekly for 3 or 4 weeks [Papadopoulos 2011]. The slower infusion likely results in better tolerability allowing for higher dosing.

The dosage and scheduling of Carfilzomib was further explored in the CHAMPION study [Berenson 2013]. Patients with relapsed or refractory MM who had received 1-3 prior regimens were treated with Carfilzomib as a 30 minute IV infusion on days 1, 8, and 15 of each 28-day cycle in combination with weekly Dexamethasone. Patients received 20 mg/m<sup>2</sup> on day 1 of cycle 1 and in this dose escalation study the maximally tolerated dose was 70 mg/m<sup>2</sup>. The higher dose Carfilzomib had an overall response rate of 67%. Additional experience with the weekly dosing strategy has been explored in the recently reported Italian trial showing similar results [Palumbo 2014].

### 2.4 Rationale for this Study

Based on the previously described potency and tolerability of a triplet-based therapy incorporating a proteasome inhibitor with a steroid-alkylator backbone and increased effectiveness of carfilzomib at higher doses we are proposing a study combining high dose weekly Carfilzomib with weekly Dexamethasone and a low dose of weekly Cyclophosphamide (CCD). We hypothesize that this combination would offer a potent yet convenient treatment option to patients with relapsed myeloma and would compare favourably with current trials examining the use of Carfilzomib in this disease. Indeed, precedent for this combination does exist. A recent open-label phase II study has demonstrated ORR of 95% and 2-year PFS and OS of 76% and 80% respectively [Brinchen 2014] albeit with the twice weekly dosing strategy. Carfilzomib has also been successfully paired with melphalan showing similar results [Moreau 2013]. Importantly, this regimen would be cost-effective; important given that the combination of carfilzomib, lenalidomide, and dexamethasone examined in the ASPIRE trial may be cost prohibitive, limiting widespread use in most of Europe and Canada.



### 3.0 BACKGROUND THERAPEUTIC INFORMATION

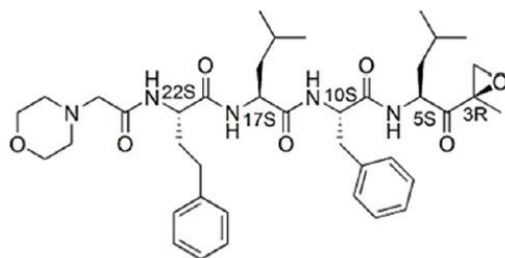
#### 3.1 Carfilzomib

##### 3.1.1 Name and Chemical Information

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbonyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide.

##### 3.1.2. Chemical Structure

The molecular formula is C<sub>40</sub>H<sub>57</sub>N<sub>5</sub>O<sub>7</sub> and the molecular weight is 719.91.



##### 3.1.3 Mechanism of Action

Carfilzomib specifically functions as an inhibitor of the CT-L activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

##### 3.1.4 Experimental Antitumour Activity

Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the 20S proteasome, primarily of the CT-L activity, and at higher concentrations, of multiple 20S proteolytic activities. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib, showed less off-target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to bortezomib; the latter showed off-target inhibitory activity in the nanomolar range against several serine proteases [Arastu-Kapur 2011]. This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in non-clinical studies comparing carfilzomib with bortezomib.

Carfilzomib primarily inhibits the CT-L activity of both the constitutive proteasome and the immunoproteasome [Demo 2007; Kuhn 2007]. The importance for co-inhibition of multiple proteasome active sites for cytotoxicity (CT-L, trypsin-like, and/or caspase-like) has been demonstrated against multiple myeloma cell lines [Britton 2009; Geurink 2013]. Nonclinical work supported improved tolerability with increased infusion time, possibly because of the reduced maximum concentration (C<sub>max</sub>) with a 30-minute IV infusion [Yang 2011]. Correlative clinical pharmacodynamics studies have confirmed that longer infusion times and higher doses of carfilzomib resulted in increased proteasome inhibition [Lee 2012; Papadopoulos 2015]. Clinical evidence for carfilzomib dose response has been observed in a multivariable modeling analysis comparing 20 mg/m<sup>2</sup> with 27 mg/m<sup>2</sup> [Squifflet 2011], suggesting that more effective inhibition of proteasome activity may improve efficacy. An increased infusion time of 30 minutes enabled carfilzomib to be administered at a higher dose with a maximum tolerated dose (MTD) of 56 mg/m<sup>2</sup> in Study PX-171-007 compared to a 27 mg/m<sup>2</sup> over a 2 to 10 minute infusion.

3.1.5 Phase I Trials of Higher Doses of Carfilzomib

CHAMPION 1, a phase Ib/II study in subjects with relapsed multiple myeloma who had received 1 to 3 prior therapies was initiated to investigate higher doses of carfilzomib given once-weekly in combination with dexamethasone, and results indicate that these modifications were well tolerated and active. In the phase Ib dose-escalation portion of the study all subjects received 20 mg/m<sup>2</sup> carfilzomib on cycle 1 day 1 and then received the cohort-assigned test dose on cycle 1 days 8 and 15. The initial dose level evaluated was 45 mg/m<sup>2</sup> with escalation to 56 mg/m<sup>2</sup>, 70 mg/m<sup>2</sup>, and 88 mg/m<sup>2</sup> in successive cohorts. Subjects received 40 mg dexamethasone on days 1, 8, 15, and 22 of cycles 1 through 8 and on days 1, 8, and 15 from cycle 9 onward.

No dose limiting toxicities (DLTs) were observed during dose escalation at the dose levels of 45 mg/m<sup>2</sup>, 56 mg/m<sup>2</sup>, or 70 mg/m<sup>2</sup>. At the carfilzomib dose level of 88 mg/m<sup>2</sup>, 2 DLTs were observed during cycle 1:

- Dyspnea (grade 3, days 9 to 11)
- Vomiting (grade 3, day 15)

Per protocol, an expansion cohort of 9 additional subjects was enrolled at the 70 mg/m<sup>2</sup> dose. There was 1 DLT in the 70 mg/m<sup>2</sup> expansion cohort: Grade 3 dyspnea (days 16 to 18). The MTD of once-weekly carfilzomib in combination with dexamethasone was determined to be 70 mg/m<sup>2</sup>.

A total of 27 subjects were enrolled in the phase I portion of the study with a median of 1 prior therapy. Fifteen subjects received study treatment at a dose of 70 mg/m<sup>2</sup>. The majority of the 27 subjects (85%) received prior bortezomib and 63% of those were refractory to bortezomib. The ORR in the phase I population was 81% with a clinical benefit rate (CBR) of 93%. The once-weekly treatment regimen of 70 mg/m<sup>2</sup> showed promising activity with an ORR of 93% (95% CI: 68.1 to 99.8%), 4 subjects achieved a complete response (CR) and the CBR was 100% (95% [CI]: 78.2 to 100%). The median treatment duration was 8.3 months in this cohort [Berenson 2014]. Five serious adverse events (SAEs) were reported in the phase I part of this ongoing study:

- One subject at 45 mg/m<sup>2</sup> had 2 SAEs; increased blood creatinine (grade 3) and hyponatremia (grade 4).
- One subject at 70 mg/m<sup>2</sup> had pneumonia (grade 3).
- One subject at 88 mg/m<sup>2</sup> had dyspnea (grade 3).
- One subject at 70 mg/m<sup>2</sup> had chronic obstructive pulmonary disease (grade 3).

All SAEs were determined to be unrelated to carfilzomib and dexamethasone except for the grade 3 dyspnea event, a DLT in a subject receiving the 88 mg/m<sup>2</sup> dose.

### 3.1.6 Phase II trials of Higher Doses of Weekly Carfilzomib

In the ongoing phase II portion of CHAMPION 1, 82 subjects have been enrolled at the MTD as of the 3 September 2014 data cutoff. The median age of subjects was 68 years with 29% of subjects  $\geq 75$  years. Subjects received a median of 1 prior regimen and 40% of subjects received 2 to 3 prior regimens. All subjects had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Most subjects (82%) had prior exposure to bortezomib; 44% were refractory to bortezomib. Over half (55%) received prior therapy with lenalidomide. Almost one-quarter of subjects had a prior transplant (27%). Subjects in the ongoing phase II expansion have received a median of 2.9 months (0.03 to 9.3) of treatment. Preliminary efficacy data from the Phase 2 portion of the study in subjects (n= 70) who were enrolled prior to 31 July 2014 demonstrate an ORR of 63%.

The most common all-grade non-hematologic AEs included fatigue (33%), nausea (22%), insomnia (21%), headache (20%), diarrhea (13%), dyspnea (13%), musculoskeletal chest pain (11%), and upper respiratory tract infection (11%).

Grade 3 AEs reported in  $> 1$  subject were; acute renal failure (5%), fatigue (5%), anemia (4%), thrombocytopenia (2%), neutropenia (2%), back pain (2%), musculoskeletal chest pain (2%), diarrhea (2%), hypoxia (2%), and atrial fibrillation (2%). A total of 34 treatment-emergent SAEs were reported in 19 subjects (23%). Six grade 4 SAEs were reported in 2 subjects (thrombocytopenia, atrial fibrillation, influenza pneumonia, respiratory failure, and septic shock [all occurred in 1 subject], and aphasia [1 subject]). Three grade 5 SAEs were reported in 3 subjects (acute renal failure, cardio-respiratory arrest, and disease progression). Four subjects (5%) discontinued treatment due to an AE and 6 subjects (7%) had a carfilzomib dose reduction due to an AE.

The preliminary results from CHAMPION 1 demonstrated that once-weekly carfilzomib at 70 mg/m<sup>2</sup> administered as a 30-minute infusion in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma had an acceptable safety and tolerability profile and promising efficacy. Ninety subjects are planned for the phase II portion of the study.

### 3.1.7 Pharmacokinetic Studies of High Dose Weekly Carfilzomib

Pharmacokinetics (PK) and pharmacodynamics (PDn) results from CHAMPION 1 are supportive of the proposal to study the once-weekly 70 mg/m<sup>2</sup> regimen as an effective alternative regimen for carfilzomib.

Preliminary PK results from CHAMPION 1 indicated that a once-weekly 30-minute infusion of carfilzomib had a mean terminal half-life similar to the half-life of  $\leq 1$  hour following the approved twice-weekly dosing regimen (20/27 mg/m<sup>2</sup> over 2 to 10 minutes). In addition, the data showed a dose-proportional increase in the mean C<sub>max</sub> and area under the curve (AUC) from 20 to 88 mg/m<sup>2</sup>, as indicated by the similar dose normalized values for C<sub>max</sub> and AUC. The AUC following a 70 mg/m<sup>2</sup> dose was 1045 ng•h/mL, which is higher than the total weekly AUC following the twice-weekly of 27 mg/m<sup>2</sup> dose (758 ng•h/mL). The mean C<sub>max</sub> following the 70 mg/m<sup>2</sup> dose administered as a 30-minute infusion is 2640 ng/mL, which is lower than the mean C<sub>max</sub> of 4232 ng/mL in Study PX-71-003 – Part 2 (A1) following the IV infusion of 27 mg/m<sup>2</sup> over 2 to 10 minutes.

### 3.1.8 Pharmaceutical Data

*Supplied:*

Carfilzomib for injection is supplied as a lyophilized parenteral product in single-use vials packaged in multi-vial cartons. Institutional pharmacies will be supplied with open stock vials with full disclosure labels. Additional details are provided in the pharmacy manual.

*Stability:*

Once carfilzomib is reconstituted and inspected, the clear solution may be stored in a refrigerator (recommended) controlled temperature from 2°C to 8°C (36°F–46°F) for up to 24 hours. Once reconstituted, carfilzomib must be used within 4 hours if not refrigerated and within 24 hours if it has been stored in a light-tight refrigerator (refer to Table 1 below).

Table 1: Storage Conditions of Reconstituted Carfilzomib

	Stability in hours per container		
	Vial	Syringe	IV Bag (D5W)
Refrigerated (2°C to 8°C; 36°F to 46°F)	24	24	24
Room temperature (15°C to 30°C; 59°F to 86°F)	4	4	4

*Storage:*

Study treatments should be stored in a securely locked area with access limited to appropriate study personnel. Carfilzomib must be stored at 2°C to 8°C (36°F–46°F) in a refrigerator. Carfilzomib vials must be kept in cartons in order to protect from light until ready for reconstitution.

*Solution Preparation:*

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib free base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-beta-cyclodextrin(SBE-CD, Captisol).

*Route of Administration:*

Intravenous

### 3.2 Cyclophosphamide

For further information on cyclophosphamide please refer to the approved package insert.

*Other Names:*

Cytosan, Procytox.

*Classification:*

Alkylating agent.

*Mechanism of Action:*

Cyclophosphamide is a nitrogen mustard of the oxazophosphorine group. It is an alkylating agent, which exerts its cytotoxic effect via 3 mechanisms: 1) attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, 2) DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and 3) the induction of mispairing of the nucleotides leading to mutations.

*Metabolism:*

Cyclophosphamide is absorbed from the gastrointestinal tract, or can be given parenterally. It is biologically relatively inactive, and is activated by hepatic cytochrome p-450 to 4-hydroperoxycyclophosphamide. This compound is in steady state with the acyclic tautomer, aldophosphamide; the drug and its metabolites are distributed throughout the body, including the brain. Cyclophosphamide is eliminated very slowly. The metabolites alkylate the target sites in cells in an "all-or-none" fashion, or are depleted by the formation of inactive metabolites that are rapidly excreted via the kidneys. The rate of metabolism of cyclophosphamide is variable among different individuals. The average half-life of unchanged drug is between 5 and 6.5 hours after an intravenous dose. The peak plasma concentrations of metabolites are proportional to the dose given, with peak levels achieved generally 2-3 hours after the drug is given.

*Route of Administration:*

Oral.

*Availability:*

Commercially available in 50 mg tablets.

*Drug interactions:*

The rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital. Cyclophosphamide also markedly inhibits cholinesterase activity, and potentiates the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

*Other Considerations (adrenalectomy):*

Since cyclophosphamide has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary in such a patient.

*Side-effects*

*Gastrointestinal:*

Nausea, vomiting, anorexia, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

*Dermatologic:*

Alopecia is common; the hair usually grows back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color. Skin rash occurs occasionally. Pigmentation of the skin and changes in nails can occur.

*Hematologic:*

Leukopenia is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/mm<sup>3</sup> is common when an initial loading dose of the drug is utilized, and less frequent in patients maintained on smaller doses. The degree of neutropenia correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients. Thrombocytopenia or anemia develops occasionally in patients treated with cyclophosphamide. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7 to 10 days after cessation of therapy.

*Urinary:*

Hemorrhagic cystitis, rarely, can be severe or even fatal. Fibrosis of the urinary bladder may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. Bladder injury is attributed to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to achieve ample urine output, promoted frequent voiding, and reduces the time the exposure of the bladder to the drug and its metabolites to help prevent cystitis. Significant hemorrhagic cystitis typically necessitates discontinuation of cyclophosphamide. Rarely, hemorrhagic ureteritis and renal tubular necrosis have been reported in patients treated with cyclophosphamide.

*Genital:*

Cyclophosphamide can cause fetal harm when administered to a pregnant woman. Its interference with oogenesis and spermatogenesis may result in sterility, potentially irreversible, in males and females.

*Cardiac:*

Several instances of cardiac dysfunction have been described following the recommended doses of cyclophosphamide; however, no causal relationship has been established. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m<sup>2</sup> to as high as 26 g/m<sup>2</sup>, most often when given as part of an intensive anti-cancer multi-drug regimen or in conjunction with transplantation procedures. In a few instances, severe, and sometimes fatal, congestive heart failure has occurred after the initial dose of high doses of cyclophosphamide. Histopathologic examination has mainly demonstrated hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of any hemopericardium. No residual cardiac abnormalities, as evidenced by electrocardiogram or echocardiogram appear to be present in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide. Cyclophosphamide has been reported to potentiate doxorubicin-induced cardiotoxicity.

*Respiratory:*

Interstitial pneumonitis has been reported; interstitial pulmonary fibrosis has also been described with prolonged cyclophosphamide use.

*Second Malignancies:*

Second malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Most frequently, they have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Second malignancies most often were diagnosed in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically.

*Other:*

Anaphylactic reactions, including fatal reactions, have been reported; possible cross-sensitivity with other alkylating agents has been described; SIADH (syndrome of inappropriate ADH secretion); appearance of serious infections including Herpes zoster, Varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing.

### 3.3 Dexamethasone

For further information on dexamethasone please refer to the approved package insert.

*Other Names:*

Decadron, Hexadrol, Dexameth, Dexone, DXM, others.

*Classification:*

Adrenal corticosteroid.

*Mechanism of Action:*

Dexamethasone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, antineoplastic, and antiemetic properties and very little mineralocorticoid activity. As an antineoplastic agent, dexamethasone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

*Storage and Stability:*

The drug is stored at room temperature in a dry place.

*Route of Administration:*

Oral.

*Availability:*

Commercially available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets.

*Side Effects:*

*Gastrointestinal:*

Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.

*Dermatologic:*

Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.

*Genitourinary:*

Menstrual changes (amenorrhea, menstrual irregularities).

*Neurologic:*

Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, and muscle weakness.

*Cardiovascular:*

Fluid retention and edema, hypertension; rarely, thrombophlebitis.

*Ocular:*

Cataracts, increased intraocular pressure, exophthalmos.

*Metabolic:*

Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

*Hematologic:*

Leukocytosis.

*Other:*

Osteoporosis (and resulting back pain), appearance of serious infections including Herpes zoster, Varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests

*Nursing / Patient Implications:*

- When administered orally, give with food or milk.
- Observe for signs of hyperglycemia.
- Observe for subtle signs of infection (fever, pain).



#### 4.0 TRIAL DESIGN

This study is an investigator initiated trial run through the Myeloma Canada Research Network with financial support from Amgen. It is a non-randomized, 76 patient multicenter single arm phase II study of carfilzomib (20 mg/m<sup>2</sup> day 1 of first cycle then escalated to 70 mg/m<sup>2</sup> for all subsequent doses) given on days 1, 8, and 15 of a 28 day cycle plus weekly oral dexamethasone 40 mg and cyclophosphamide 300 mg/m<sup>2</sup> capped at 500 mg. This study will be restricted to patients who have had at least one, but not more than three, prior lines of therapy. Treatment duration will be until progression or intolerance, except for cyclophosphamide which will be discontinued after a maximum of 1 year.

The study will begin with a 6 patient lead-in phase where safety at 70 mg/m<sup>2</sup> will be evaluated in real time. If no safety concerns are identified, the tested dose will be expanded to add an additional 63 patients. If safety concerns are observed in more than 1 out of 6 patients, then the carfilzomib dose will be administered at 56 mg/m<sup>2</sup> (20 mg/m<sup>2</sup> on day 1 then escalated to 56 mg/m<sup>2</sup> for day 8 and 15) during the first cycle in the expansion cohort and then escalated to 70 mg/m<sup>2</sup> starting with cycle 2 provided that there are no related grade 2 or higher non-hematologic or grade 3 or higher hematologic toxicities during the first cycle. Non-evaluable patients (up to 7) will be replaced for a total planned accrual of approximately 76 patients.

Safety Concerns are defined as:

- Inability to begin cycle 2 because of drug-related toxicity;
- Grade 2 or higher neuropathy with pain;
- Any drug related grade 3 or higher non-hematologic adverse event (excluding nausea, vomiting, diarrhea, dexamethasone-induced hyperglycemia);
- Any toxicity requiring dose reduction within cycle 1;
- Grade 4 neutropenia ( $ANC < 0.5 \times 10^9/L$ ) lasting longer than 7 days despite intervention;
- Febrile neutropenia ( $ANC < 1.0 \times 10^9/L$  with fever  $\geq 38^\circ C$ );
- Grade 4 thrombocytopenia (platelets  $< 25 \times 10^9/L$ ) longer than 7 days and requiring platelet transfusion;
- Grade 3 thrombocytopenia associated with bleeding.

## 5.0 STUDY POPULATION

Enrolled patients must meet standard diagnostic criteria for multiple myeloma and they must have relapsed disease according to the International Myeloma Working group criteria [Palumbo 2009]. Prior autologous stem cell transplant is allowed but not required. This study will be restricted to patients who have had at least one, but not more than three, prior lines of therapy. Previous treatment with bortezomib is permitted, but refractory patients (relapsed within 60 days of last bortezomib dose) will be excluded.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

### 5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria should be addressed prior to calling for registration.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

#### 5.1.1 Disease Related

5.1.1.1 Relapsed symptomatic multiple myeloma as per the International Myeloma Working group criteria [Palumbo 2009].

5.1.1.2 Measurable disease, as defined by one or more of the following (assessed within 21 days prior to registration):

- Serum M-protein  $\geq 5$  g/L (0.5g/dL)
- Urine Bence-Jones protein  $\geq 200$  mg/24 hours
- Involved serum free light chain (FLC) measurement  $\geq 100$  mg/L (10 mg/dL), provided serum FLC ratio is abnormal (abnormal if FLC ratio is  $<0.26$  or  $>1.65$ )
- Biopsy proven plasmacytoma
- For IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA)  $\geq 750$  mg/dL (0.75 g/dL)

5.1.1.3 Prior treatment with at least one, but no more than three, regimens for multiple myeloma.

5.1.1.4 Documented relapse or progressive disease on or after any regimen (subjects refractory to the most recent line of therapy are eligible except those who are refractory to bortezomib as described in exclusion criteria 1).

5.1.1.5 Achieved a response to at least one prior regimen (defined as  $\geq 25\%$  decrease in M-protein).

5.1.2 Demographic

5.1.2.1 Age  $\geq$  18 years.

5.1.2.2 Life expectancy  $\geq$  3 months.

5.1.2.3 ECOG performance status 0–2.

5.1.3 Laboratory Requirements (must be done within 21 days of registration):

*Hematology:*

- Absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/L$
- Hemoglobin  $\geq 8$  g/dL (80 g/L) (subjects may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines)
- Platelet count  $\geq 50 \times 10^9/L$ , independent of platelet transfusion for 7 days ( $\geq 30 \times 10^9/L$  if myeloma involvement in the bone marrow is  $\geq 50\%$ )

*Biochemistry:*

- ALT  $\leq 3.5 \times$  UNL
- Serum direct bilirubin  $\leq 2$  mg/dL (34  $\mu\text{mol/L}$ ) (only required if total bilirubin  $\geq 2$  mg/dL (34  $\mu\text{mol/L}$ ))
- Creatinine clearance (CrCl)  $\geq 30$  mL/minute (Cockcroft and Gault formula) and not on dialysis

5.1.4 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

5.1.5 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CRO office at 613-533-6430 if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

5.1.6 In accordance with CRO policy, protocol treatment is to begin within 2 working days of patient registration.

5.1.7 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method as detailed in Section 8.2.8.

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## 5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

### 5.2.1 Disease-Related

#### 5.2.1.1 Refractory to any proteasome inhibitor therapy (bortezomib, ixazomib, etc.)

Refractory disease is defined as failure to respond to the proteasome inhibitor, initial response followed by progression while on a proteasome inhibitor, or relapse within 60 days of stopping proteasome inhibitor therapy

#### 5.2.1.2 Prior carfilzomib treatment.

#### 5.2.1.3 POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

#### 5.2.1.4 Waldenström's macroglobulinemia or IgM myeloma

#### 5.2.1.5 Current or previous plasma cell leukemia(defined as $> 2.0 \times 10^9/L$ circulating plasma cells by standard differential)

### 5.2.2 Concurrent Treatments

#### 5.2.2.1 Chemotherapy or investigational agent within 3 weeks prior to registration or antibody therapy within 6 weeks prior to registration

#### 5.2.2.2 Radiotherapy to multiple sites within 28 days prior to registration; localized radiotherapy to a single site within 7 days prior to registration

#### 5.2.2.3 Plasmapheresis within 14 days of registration.

### 5.2.3 Concurrent Conditions

#### 5.2.3.1 Pregnant or lactating females.

#### 5.2.3.2 Major surgery within 21 days prior to registration.

#### 5.2.3.3 Active, uncontrolled bacterial, fungal, or viral infection

#### 5.2.3.4 Known human immunodeficiency virus infection.

#### 5.2.3.5 Active hepatitis B or C infection.

#### 5.2.3.6 Myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or grade 3 conduction system abnormalities unless subject has a pacemaker.

#### 5.2.3.7 Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration.

5.2.3.8 Concurrent amyloidosis.

5.2.3.9 Other malignancy, including MDS, within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels; or cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumours of the adrenal or pancreas.

5.2.3.10 Significant neuropathy ( $\geq$  grade 3, or grade 2 with pain) within 14 days prior to registration.

5.2.3.11 Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).

5.2.3.12 Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment.

5.2.3.13 Ongoing graft-versus-host disease.

5.2.3.14 Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration.

5.2.3.15 Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

6.0 PRE-TREATMENT EVALUATION  
(See Table 2 and Appendix I)

Table 2: Pre-Treatment Evaluation

Investigations		Timing
History and Physical Exam including:	<u>History, including:</u> <ul style="list-style-type: none"> <li>diagnosis of myeloma</li> <li>prior therapy, concurrent illness / medications</li> <li>review of symptoms</li> <li>demographics</li> </ul> <u>Physical Exam, including:</u> <ul style="list-style-type: none"> <li>height and weight, BSA, performance status</li> <li>vital signs</li> <li>complete exam including neurological and plasmacytoma assessment (if appropriate)</li> </ul>	Within 21 days prior to registration
Hematology	<ul style="list-style-type: none"> <li>CBC and differential</li> </ul>	
Biochemistry	<u>Full serum chemistry panel:</u> <ul style="list-style-type: none"> <li>BUN</li> <li>creatinine</li> <li>glucose (random)</li> <li>uric acid</li> <li>bicarbonate</li> <li>calcium</li> <li>chloride</li> <li>phosphorus</li> <li>potassium</li> <li>sodium</li> <li>LDH</li> <li>albumin</li> <li>total protein</li> <li>magnesium</li> <li>total bilirubin</li> <li>serum direct bilirubin*</li> <li>alkaline phosphatase</li> <li>ALT and AST</li> </ul>	Within 30 days prior to registration
Radiology	<ul style="list-style-type: none"> <li>Skeletal survey (including skull, all long bones, pelvis and chest)</li> <li>Extra-medullary plasmacytomas should be assessed by either PET/CT scan, CT or MRI, whichever is most appropriate for the location of the lesion**</li> </ul>	
Other Investigations	<ul style="list-style-type: none"> <li>Serum Pregnancy test (For women of childbearing potential only)</li> </ul>	Within 72 hours prior to registration
	<ul style="list-style-type: none"> <li>Cytogenetic assessment of marrow plasma cells by FISH for t(4;14), t(14;16), del P53 to be done as per local standard***</li> </ul>	Within 8 weeks prior to registration
	<ul style="list-style-type: none"> <li>Urinalysis including macroscopic examination (specific gravity, protein, pH, glucose, ketones, blood, leukocyte esterase and nitrite)</li> <li>Urinalysis with microscopic examination (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast)</li> <li>24-hour urine protein with urine protein electrophoresis (UPEP)* and urine immunofixation electrophoresis (UIFE)</li> <li>Serum protein electrophoresis (SPEP) with immunofixation to confirm monoclonal protein sub-type</li> <li>Serum free light chain (sFLC)</li> <li>Serum <math>\beta</math>2-microglobulin</li> <li>Quantitative immunoglobulins</li> <li>12-lead ECG with QTC interval</li> </ul>	Within 21 days of registration
	<ul style="list-style-type: none"> <li>Bone Marrow aspiration and biopsy for baseline assessment of plasma cell burden.</li> </ul>	
	Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	Within 21 days of registration
<p>* Only required if total bilirubin <math>\geq 2</math> mg/dL (34 <math>\mu</math>mol/L)  ** Only required if plasmacytomas are being followed  *** Patients can be enrolled prior to cytogenetics results.  ♦ 24 hour assessment, no substitute method is acceptable</p>		

## 7.0 ENTRY/REGISTRATION PROCEDURES

### 7.1 Entry Procedures

All registration will be done through the CRO web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the “EDC Data Management Guidebook”, posted on the MYX.1 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the MYX.1 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CRO.

The following information will be required:

- trial code (MYX.1)
- investigator user ID
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- body surface area (BSA), height and weight

### 7.2 Body Surface Area Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m<sup>2</sup> or less. Subjects with a BSA > 2.2 m<sup>2</sup> will receive a dose based upon a 2.2 m<sup>2</sup> BSA. BSA calculations are based on the DuBois formula:

$$\text{BSA (m}^2\text{)} = (\text{W(kg)}^{0.425} \times \text{H (m)}^{0.725}) \times 0.007184.$$

### 7.3 Registration

Registration will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the followup of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration.

All randomized patients are to be followed until death or until sites are informed by CRO that further follow-up is no longer required. The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the baseline Report. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

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## 8.0 TREATMENT PLAN

Although the CRO acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CRO policy, protocol treatment is to begin within 2 working days of patient registration.

### 8.1 Chemotherapy Treatment Plan

#### 8.1.1 Drug Administration

Table 3. Treatment Schedule

Agent(s)	Dose	Route	Duration	Schedule
Carfilzomib	20 mg/m <sup>2</sup> (cycle 1, day 1 only)	IV	30 mins	D1, D8, D15 of each cycle*
	70 mg/m <sup>2</sup> (all subsequent doses)			
Cyclophosphamide	300 mg/m <sup>2</sup> **	PO	--	D1, D8, D15, D22 of each cycle
Dexamethasone	Age < 70 years, 40 mg Age ≥ 70 years, 20 mg	PO	--	D1, D8, D15, D22 of each cycle
* 1 cycle = 28 days				
** Capped at 500 mg, see 8.1.1.2 for further details				

Carfilzomib, cyclophosphamide and dexamethasone will be administered in 28-day cycles. All cycles will start 28 days (± 2) after the start of the prior cycle. Once-weekly carfilzomib must never be administered within the 5 days following a previous carfilzomib infusion.

The reason for all cycle delays, missed doses, and dose interruptions will be reported.

- 8.1.1.1 Carfilzomib will be administered as an IV infusion over approximately 30 minutes. Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Sterile Water for Injection (SWI), United States Pharmacopeia (USP), to a final carfilzomib concentration of 2.0 mg/mL prior to administration. The dose can be calculated using the subject's actual body surface area (BSA) at baseline; however, dosing adjustments for subsequent actual BSA determinations are allowed per institutional guidelines. Subjects with a BSA > 2.2 m<sup>2</sup> will receive a dose based upon a 2.2 m<sup>2</sup> BSA. Dose adjustments must be made for weight gains/losses of ≥ 10% of baseline body weight.

Mechanical infusion pumps are recommended but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained. Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions. Subjects will remain at the investigational site under observation for at least 1 hour following each infusion of carfilzomib in cycle 1. Carfilzomib should be administered via a dedicated IV line. If an existing IV line or permanent infusion device (e.g. porta-cath) is used for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline or 5% Dextrose Injection (D5W), prior to and following carfilzomib infusion.



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- 8.1.1.2 Cyclophosphamide tablets will be given orally at a dose of 300 mg/m<sup>2</sup> on the days 1, 8, 15 and 22 each cycle. The dose be rounded off to the closest 50 mg and will be capped at 500 mg total per week. It is recommended the dose be administered any time prior to carfilzomib administration on corresponding days. After 1 year (12 cycles) of therapy the cyclophosphamide will be discontinued.
- 8.1.1.3 Dexamethasone will be taken orally. It is recommended dexamethasone be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib infusion on days 1, 8 and 15. It will be given again on day 22 with cyclophosphamide.

8.1.2 IV Hydration

Subjects will receive IV prehydration prior to each carfilzomib infusion during cycle 1. Prehydration will consist of 250 mL normal saline or other appropriate IV fluid. Thereafter, carfilzomib prehydration should only be administered if the subject's condition and/or risk factors require hydration. The total amount of prehydration will be reported and the reason for hydration after cycle 1 will be reported.

Adequate hydration is required prior to dosing in cycle 1, especially in subjects at high risk of tumour lysis syndrome (TLS) or renal toxicity. All subjects should be monitored for evidence of volume overload and fluid requirements should be tailored to individual subject needs. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at high risk for cardiac failure.

8.1.3 Premedication

It is strongly encouraged but not required that all patients will be premedicated with ondansetron 8-16 mg PO once daily on days 1, 8, 15, and 22 at least 30 minutes before chemotherapy administration.

8.1.4 Prophylactic Medications

Required prophylactic medications should be initiated at least 24 hours prior to the first administration of carfilzomib.

8.1.4.1 Antiviral Prophylaxis: Acyclovir (or an equivalent antiviral) is a required concomitant medication.

Acyclovir 400 mg PO BID (or equivalent antiviral according to institutional practice), should be continued for the duration of study treatment. If valacyclovir is used it should be given at 500 mg PO daily. Additional prophylaxis is at the investigator's discretion.

8.1.4.2 Gastrointestinal Prophylaxis: Lansoprazole, 15 mg PO daily, or other oral proton-pump inhibitor according to institutional practice to prevent peptic ulcer disease is a required concomitant medication throughout the duration of study treatment with dexamethasone.

8.1.5 Duration of Protocol Treatment

Therapy is delivered weekly until the criteria for removal from protocol treatment have been met (see Section 12.0).

## 8.2 Patient Monitoring

### Special Warnings and Precautions for Use

#### *Cardiopulmonary Disorders:*

New or worsening cardiac failure (e.g. congestive cardiac heart failure, pulmonary edema, and decreased ejection fraction), myocardial ischemia, and myocardial infarction have occurred following administration of carfilzomib. Death due to cardiac arrest has occurred within a day of carfilzomib administration, and fatal outcomes have been reported with cardiac failure and myocardial infarction.

#### *Acute Renal Failure:*

Cases of acute renal failure have been reported in subjects who received carfilzomib. Acute renal failure was reported more frequently in subjects with advanced relapsed and refractory multiple myeloma who received carfilzomib monotherapy. This risk was increased in subjects with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving carfilzomib.

#### *Tumour Lysis Syndrome:*

Cases of tumour lysis syndrome (TLS), including fatal outcome, have been reported in subjects who received carfilzomib. Subjects with a high tumour burden should be considered to be at greater risk for TLS. Ensure that subjects are well hydrated before administration of carfilzomib in cycle 1 and in subsequent cycles as needed. Uric acid-lowering drugs should be considered in subjects at high risk for TLS. Monitor for evidence of TLS during treatment, including regular measurement of serum electrolytes, and manage promptly. Interrupt carfilzomib until TLS is resolved.

#### *Infusion Reactions:*

Infusion reactions, including life-threatening reactions, have been reported in subjects who received carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Administer dexamethasone prior to carfilzomib either as premedication or as part of combination therapy to reduce the incidence and severity of reactions.

#### *Thrombocytopenia:*

Carfilzomib causes thrombocytopenia with platelet nadirs observed between day 8 and day 15 of each 28-day cycle with recovery to baseline platelet count by the start of the next cycle.

#### *Hepatic Toxicity:*

Cases of hepatic failure, including fatal cases, have been reported. Carfilzomib can cause elevations of serum transaminases.

#### *Thrombocytopenic Thrombotic Purpura / Hemolytic Uremic Syndrome:*

Cases of thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS) including those with fatal outcome have been reported in subjects who received carfilzomib. Monitor for signs and symptoms of TTP/HUS. The safety of reinitiating carfilzomib therapy in subjects previously experiencing TTP/HUS is not known.

*Posterior Reversible Encephalopathy Syndrome:*

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension. The diagnosis is confirmed by neuro-radiological imaging. If diagnosed early and treated, the symptoms of PRES may be reversed. Cases of PRES have been reported in subjects receiving carfilzomib. The safety of reinitiating carfilzomib therapy in subjects previously experiencing PRES is not known.

*Overdose:*

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia have been reported following a dose of 200 mg of carfilzomib administered in error. There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the subject should be monitored.

*Geriatric Use:*

Overall, the subject incidence of certain adverse events (including cardiac failure) in clinical trials was higher for subjects who were  $\geq 75$  years of age compared to subjects who were  $< 75$  years of age.

8.2.1 Dose Adjustments

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

There will be no re-escalation of dose after reduction for adverse events unless otherwise specified in the dose modification tables below.

- 8.2.2 The major toxic effects which will limit the dose of carfilzomib are listed in Tables 4 and 6. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

8.2.3 Carfilzomib Dose Decrements

Dose	Carfilzomib Dose Decrements		
	First Dose Reduction Dose -1	Second Dose Reduction Dose -2	Third Dose Reduction Dose -3
70 mg/m <sup>2</sup>	56 mg/m <sup>2</sup>	45 mg/m <sup>2</sup>	36 mg/m <sup>2</sup>

8.2.4 Hematologic Adverse Events

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V). Guidelines for dose modification of carfilzomib and cyclophosphamide in the event of hematologic toxicities are summarized in Table 4.

**Table 4: Dosing Guidelines for Hematologic Toxicity**

Hematologic Toxicity	Recommended Action*	
	Carfilzomib	Cyclophosphamide
<b>Thrombocytopenia</b>		
If platelets $10 - 30 \times 10^9/L$ without evidence of bleeding**	Go down by one dose decrement***	Continue at 50% dose reduction
If evidence of bleeding or platelets $< 10 \times 10^9/L$	Withhold dose until platelets return to $\geq 10 \times 10^9/L$ and/or bleeding is controlled, then reduce by one dose decrement**	Withhold dose until platelets return to $\geq 10 \times 10^9/L$ , then resume at 50% dose reduction
<b>Neutropenia</b>		
If ANC $< 0.5 \times 10^9/L$	Withhold dose until ANC returns to $\geq 0.5 \times 10^9/L$ , then resume at same dose	Withhold dose until ANC returns to $\geq 0.5 \times 10^9/L$ , then resume at 50% reduction.
ANC = absolute neutrophil count; * The maximum allowed dose interruption is 4 weeks. ** Support with platelet transfusion is allowable to maintain platelets at $> 20 \times 10^9/L$ *** See Carfilzomib Dose Decrements table above.		

#### 8.2.5 Non-Hematologic Adverse Events

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V). Guidelines for dose modification in the event of non-hematologic toxicities are summarized in Table 5.

**Table 5: Carfilzomib Dosing Guidelines for Non-Hematologic Toxicity**

Non-Hematologic Toxicity	Recommended Action*
<b>Renal Dysfunction</b>	
Serum creatinine equal to or greater than $2 \times$ baseline, or CrCl $< 15$ mL/min (or CrCl decreases to $\leq 50\%$ of baseline), or need for dialysis	<ul style="list-style-type: none"> <li>Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance).</li> <li>If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction.</li> <li>If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician.</li> <li>If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.</li> </ul>
<b>Hepatic Dysfunction</b>	
$\geq$ Grade 3 Elevation in LFTs (AST, ALT, or total bilirubin)**	Withhold dose. Resume at 1 dose decrement when toxicity has resolved to baseline***
<b>Non-neutropenic infection</b>	
Grade 3 Infection	Withhold carfilzomib until infection resolves. Resume carfilzomib at same dose.

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**Table 5: Carfilzomib Dosing Guidelines for Non-Hematologic Toxicity** *continued*

Non-Hematologic Toxicity	Recommended Action*
<b>Cardiac toxicity</b>	
Congestive heart failure	<ul style="list-style-type: none"> <li>Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued.</li> <li>If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.</li> </ul>
Left Ventricular Ejection Fraction Reduction: For resting LVEF < 40% or reduction of LVEF to < 55% if the drop is greater than 20% from baseline	Withhold until LVEF returns to > 40% or, if held due to a drop to < 55%, to within 15% of baseline. Resume at 1 dose decrement.***
Other grade 3 or 4 cardiac event	Withhold carfilzomib until recovery. If recovery within 4 weeks may be restarted at one dose level reduction. If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.
<b>Micro-Angiopathy</b>	
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	<ul style="list-style-type: none"> <li>If suspected TTP/HUS, withhold carfilzomib.</li> <li>Manage symptoms per standard of care including plasma exchange as clinically indicated.</li> <li>If the diagnosis of TTP/HUS is excluded, carfilzomib administration may resume if clinically appropriate.</li> </ul>
<b>Other</b>	
Pulmonary Hypertension	<ul style="list-style-type: none"> <li>Withhold until resolved or returned to baseline.</li> <li>Restart at the dose used prior to the event or reduce dose by 1 dose level (i.e. 70 mg/m<sup>2</sup> to 56 mg/m<sup>2</sup> for the once weekly schedule), at the discretion of the physician.</li> <li>If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.</li> </ul>
Posterior reversible encephalopathy syndrome (PRES; with symptoms including headaches, altered mental status, seizures, visual loss, and hypertension)	<ul style="list-style-type: none"> <li>If suspected PRES, withhold carfilzomib.</li> <li>Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES.</li> <li>If the diagnosis of PRES is excluded, carfilzomib administration may resume if clinically appropriate.</li> </ul>
Any Other Drug-Related Non-Hematologic Toxicity ≥ Grade 3	<ul style="list-style-type: none"> <li>For carfilzomib attribution, withhold dose.</li> <li>Resume at 1 dose decrement when toxicity has resolved to grade 2 or less or to baseline grade.</li> <li>If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.</li> </ul>
<p>ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; IB = Investigator's Brochure; LFTs = liver function tests; LVEF = left ventricular ejection fraction; mL = milliliter(s); ULN = upper limit of normal. Note: Carfilzomib dose schedule does not need to be adjusted for baseline renal dysfunction. * The maximum allowed dose interruption is 4 weeks. ** If AST or ALT is ≥ 3 × ULN, report as serious adverse event (SAE), see section 11.1. *** Dose reduction should be attempted first to manage treatment-emergent toxicities.</p>	

## 8.2.6 Dexamethasone

Dose reduction levels of dexamethasone for toxicity management of individual subjects are provided in Table 6.

**Table 6:** Dose Decrements for Dexamethasone

Nominal Dose	Dexamethasone Dose Decrements	
	Dose -1	Dose -2
40 mg	20 mg	12 mg

Dexamethasone will be permanently discontinued after 2-dose level reductions in the event of additional dexamethasone-related toxicities. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. Guidelines for dexamethasone-related toxicities are summarized in Table 7.

**Table 7:** Treatment Guidelines for Dexamethasone-related Toxicities

Symptom	Findings	Recommended Action
Cardiovascular	Edema > grade 3 (anasarca or limiting function and unresponsive to therapy)	<ul style="list-style-type: none"> <li>Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement.</li> <li>Discontinue dexamethasone permanently if symptoms persist despite second reduction.</li> </ul>
Gastrointestinal Toxicity	Dyspepsia, gastric or duodenal ulcer, or gastritis grade 1 or 2 (requiring medical management)	<ul style="list-style-type: none"> <li>Continue dexamethasone at same dose and treat with therapeutic doses of histamine 2 (H2) blockers, or proton pump inhibitor.</li> <li>Consider adding sucralfate or other antiulcer treatment as clinically indicated.</li> <li>If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.</li> </ul>
	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥ grade 3 (requiring hospitalization or surgery)	<ul style="list-style-type: none"> <li>Withhold dexamethasone until symptoms return to baseline.</li> <li>Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole.</li> <li>If symptoms persist despite above measures, discontinue dexamethasone permanently.</li> </ul>
	Acute pancreatitis	<ul style="list-style-type: none"> <li>Discontinue dexamethasone permanently.</li> </ul>
General Disorders	Limb edema > grade 3 (> 30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living)	<ul style="list-style-type: none"> <li>Withhold dexamethasone until symptoms return to baseline.</li> <li>Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement.</li> <li>Discontinue dexamethasone permanently if symptoms persist despite second reduction.</li> </ul>
Psychiatric Disorders	Confusion or mood alteration ≥ grade 2 (interfering with function ± interfering with activities of daily living)	<ul style="list-style-type: none"> <li>Withhold dexamethasone until symptoms return to baseline.</li> <li>Restart dexamethasone at 1 dose decrement.</li> <li>If symptoms persist despite above measures, reduce by another dose decrement.</li> </ul>

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**Table 7:** Treatment Guidelines for Dexamethasone-related Toxicities *continued*

Symptom	Findings	Recommended Action
Musculoskeletal	Muscle weakness $\geq$ grade 2 (symptomatic and interfering with function $\pm$ interfering with activities of daily living)	<ul style="list-style-type: none"> <li>Decrease dexamethasone by 1 dose decrement.</li> <li>If weakness persists, decrease dose by another dose decrement.</li> <li>Discontinue dexamethasone permanently if symptoms persist.</li> </ul>
Metabolism and Nutrition Disorders	Hyperglycemia $\geq$ grade 3 (fasting glucose $> 250$ mg/dL)	<ul style="list-style-type: none"> <li>Withhold dexamethasone until glucose is <math>\leq</math> grade 2 (<math>&lt; 250</math> mg/dL) and treat with insulin or other hypoglycemic agents as needed.</li> <li>If uncontrolled despite above measures, decrease dose by 1 dose decrement until <math>\leq</math> grade 2 (<math>&lt; 250</math> mg/dL).</li> </ul>
All Other	Other toxicity $\geq$ grade 3 felt related to dexamethasone	<ul style="list-style-type: none"> <li>Withhold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to <math>\leq</math> grade 2.</li> <li>If toxicity recurs, withhold dexamethasone dose until toxicity has resolved to <math>\leq</math> grade 2 and resume dexamethasone dose by another dose decrement.</li> <li>If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.</li> </ul>

#### 8.2.7 Cyclophosphamide

Dose reductions for cyclophosphamide will only be mandated with the development of grade 3 or 4 non-hematologic toxicity as defined by the NCI Toxicity Grade (see Appendix V). Dose reduction levels of cyclophosphamide for non-hematologic toxicity are provided in Table 8. For hematologic toxicity guidelines please see Table 4.

**Table 8:** Cyclophosphamide Dose Adjustments for non-hematologic toxicity

Study Drug	NCI Toxicity Grade	Toxicity and Action
Cyclophosphamide	Grade 3	<ul style="list-style-type: none"> <li>If, within 2 weeks, the toxicity returns to <math>\leq</math> grade 2, restart the drug at 50% of the previous dose level. If the same toxicity persists, reduce dose by an additional 50%. If the patient cannot tolerate the 75 mg/m<sup>2</sup> weekly dose, the patient will be taken off the study.</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>For any toxicity of grade 4 that is deemed likely to be related to cyclophosphamide, study drug should be withheld and the local PI notified immediately.</li> </ul>
<b>Patients who develop hematuria of any grade must have the study drugs held until the etiology can be ascertained. If the hematuria is due to a urinary tract infection and resolves with appropriate antibiotic treatment, the study drugs may be restarted at the previous dose levels. If the patient is felt to have cyclophosphamide-induced hemorrhagic cystitis, he/she will be taken off study.</b>		

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8.2.8 Pregnancy and Contraception During Dose Interruptions

In women, contraception must continue during study drug dose interruption intervals until 6 months after the last administration of cyclophosphamide, and 30 days after the last dose of carfilzomib, whichever is longest. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. If a menstrual period in a Female of Childbearing Potential (FCBP) does not occur at the anticipated time, study drug treatment must be interrupted, and a serum pregnancy test must be performed locally. Study drug administration may resume after documentation of a non-pregnant state.

Contraception for men must also continue during study drug dose interruption intervals until 6 months after the last administration of cyclophosphamide, and 90 days after the last dose of carfilzomib, whichever is longest. Male subjects must agree to refrain from donating sperm during treatment with carfilzomib and for at least 90 days after the last dose of carfilzomib.

In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy / vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

8.2.9 Duration of Therapy

Patients will continue all components of the regimen until relapse or intolerance for one year. After one year of therapy the cyclophosphamide will be discontinued but the patients will continue on carfilzomib and dexamethasone maintenance.

8.2.10 Patient Compliance

Standard assessment by study nurse will be done at each visit to assess and record patient compliance with both oral and infusional medications.

A patient diary for cyclophosphamide and dexamethasone administration should be provided to patients, in order to document compliance with protocol therapy

8.3 Concomitant Therapy

8.3.1 Permitted

Other supportive concomitant medications are allowed.

Allopurinol (or other approved uric acid-lowering agent) in subjects at high risk for tumour lysis syndrome (TLS) due to high tumour burden may be prescribed at the investigator's discretion. Subjects should be well hydrated to reduce the risk of TLS and decline in renal function.

Mycostatin or oral fluconazole to prevent oral thrush is optional and may be given at the investigator's discretion.

Subjects may receive additional antiemetics and antidiarrheal agents as necessary.



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Myeloid growth factors may be used if neutropenia occurs in accordance with local practice guidelines but should not be given prophylactically.

Subjects may receive RBC transfusions, erythropoietic stimulating agents, or platelet transfusions if clinically indicated in accordance with institutional guidelines.

Subjects may receive bisphosphonates.

Palliative radiation for pain management is permitted with the written approval of the study medical monitor.

Dexamethasone 40 mg for 4 days or equivalent is permitted prior to Cycle 1 Day 1, but only after all screening investigations including bone marrow are completed.

### 8.3.2 Not permitted

The clinical investigator should contact the study medical monitor if concomitant use of excluded medications or therapies is required, to determine the appropriateness of continued study treatment administration.

Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large marrow reserves for either a palliative or therapeutic intent is prohibited.

Additionally, no alternative or investigational anticancer therapy (other than that received in the study) is allowed prior to documentation of PD per protocol-specified disease response criteria. Any new anticancer therapies a subject received during the study (from registration to study completion or early discontinuation) must be recorded in the designated eCRF.

Corticosteroids for nonmalignant conditions (e.g. asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 20 mg/day are not permitted. Higher steroid doses given short term for exacerbations of nonmalignant conditions (e.g. asthma flare) are permitted with the approval of the study medical monitor.

Subjects requiring the use of excluded concomitant medications or procedures will be withdrawn from study treatment.

Plasmapheresis is not permitted while the subject is receiving study treatment. For subjects requiring plasmapheresis while on study treatment every attempt should be made to document disease status by IMWG criteria first, and then discontinue study treatment and monitor for survival and PFS.

Subjects requiring plasmapheresis must have 2 serum samples (for serum protein electrophoresis [SPEP] and immunofixation) and at least one 24-hour urine sample (urine protein electrophoresis [UPEP] and immunofixation) obtained prior to the procedure.

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## 9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

The following parameters will be required during and after protocol treatment to establish response as well survival endpoints.

### 9.1 Evaluation During Protocol Treatment

Patients will be evaluated as per the schedule below (Table 9).

Table 9: Schedule of Evaluation *During* Protocol Treatment

Investigations		During Treatment
History and Physical Exam including:	<ul style="list-style-type: none"> <li>weight, BSA, performance status</li> <li>review of symptoms</li> <li>complete exam including neurological and plasmacytoma assessment* (if appropriate).</li> </ul>	Day 1 of each cycle
Hematology	<ul style="list-style-type: none"> <li>CBC and differential</li> </ul>	Day 1 and 15 of cycles 1 <sup>a</sup> and 2 then day 1 of each cycle thereafter
Biochemistry	<i>Full serum chemistry panel:</i> <ul style="list-style-type: none"> <li>BUN</li> <li>creatinine</li> <li>glucose (random)**</li> <li>uric acid</li> <li>bicarbonate</li> <li>calcium</li> <li>chloride</li> <li>phosphorus</li> <li>potassium</li> <li>sodium</li> <li>LDH</li> <li>albumin</li> <li>total protein</li> <li>magnesium</li> <li>total bilirubin</li> <li>alkaline phosphatase</li> <li>ALT, AST</li> </ul>	Day 1 of cycles 1 <sup>a</sup> , 2, and 3
	<i>Abbreviated serum chemistry panel I:</i> <ul style="list-style-type: none"> <li>BUN</li> <li>creatinine</li> <li>glucose (random) **</li> <li>uric acid</li> <li>bicarbonate</li> <li>calcium</li> <li>chloride</li> <li>phosphorus</li> <li>potassium</li> <li>sodium</li> <li>LDH</li> </ul>	Days 15 of cycles 1 and 2 only

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**Table 9:** Schedule of Evaluation *During* Protocol Treatment - *continued*

Investigations		During Treatment
Biochemistry <i>continued</i>	<b>Abbreviated serum chemistry panel II:</b> <ul style="list-style-type: none"> <li>• creatinine</li> <li>• glucose (random) **</li> <li>• calcium</li> <li>• albumin</li> <li>• bicarbonate</li> <li>• potassium</li> <li>• sodium</li> <li>• chloride</li> <li>• total protein</li> <li>• total bilirubin</li> <li>• serum direct bilirubin ***</li> <li>• alkaline phosphatase</li> <li>• ALT, AST</li> </ul>	Day 1 of each cycle starting with cycle 4
Radiology <i>To ensure comparability, the baseline exams/ scans and subsequent exams/ scans to assess response must be performed using identical techniques.</i>	• Skeletal survey (including skull, all long bones, pelvis and chest)	As clinically indicated
	• Extra-medullary plasmacytomas should be assessed by CT, PET/CT scan or MRI	Only required to confirm CR or better, or to confirm PD.
Other investigations, including disease assessment	<ul style="list-style-type: none"> <li>• SPEP and immunofixation (<i>if required to confirm CR</i>)</li> <li>• Serum Free Light Chain assay (sFLC)</li> <li>• 24-hour urine protein with urine protein electrophoresis (UPEP) ♦ and urine immunofixation electrophoresis (UIFE) ♦♦</li> <li>• Quantitative immunoglobulins</li> <li>• Serum Pregnancy test (<i>for women of childbearing potential only</i>)</li> </ul>	Day1 of each cycle ♦♦♦
	• Bone marrow and aspirate	Only required to confirm CR and sCR
Adverse Events	Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).	Day1 of each cycle and then at each patient encounter within cycle
Concomitant Medications	• Concomitant medication evaluation ( <i>to document changes from previous therapy and study entry</i> )	Day1 of each cycle and then at each patient encounter within cycle
<p>α Not required at Day 1, Cycle 1 if blood work at screening was completed within 7 days of D1C1.</p> <p>* Only required to confirm CR or better, or to confirm PD.</p> <p>** If elevated perform fasting blood glucose to determine CTCAE grade and dose alterations as per Section 8.</p> <p>*** Only required if total bilirubin <math>\geq 2</math> mg/dL (34 <math>\mu</math>mol/L)</p> <p>♦ 24 hour assessment, no substitute method is acceptable.</p> <p>♦♦ Only if UPEP <math>\geq 200</math> mg/24 hours at baseline. Please note that UPEP and immunofixation is required to be completed to confirm VGPR (when serum and urine M-protein are not measurable), CR and sCR even if UPEP &lt; 200 mg/24 hours at baseline. See Table 11 of the protocol for more information.</p> <p>♦♦♦ Not required at Day 1, Cycle 1 if myeloma assessments at screening were completed within 7 days from D1C1.</p>		

## 9.2 Evaluation After Protocol Treatment

All patients who have received any protocol therapy will be seen at 4 weeks after completion of protocol treatment (end of protocol therapy). Adverse Events deemed related to protocol therapy should be assessed at the 4 week post treatment visit.

Patients who discontinue therapy due to toxicity in the absence of progression should be followed every 4 weeks until progression, or initiation of non-protocol therapy for the first 3 months after end of treatment. Following 3 months after the end of treatment, patients can be followed every 3 months. A Follow up Report should be used to capture follow-up information prior to progression.

After relapse, progression or initiation of non-protocol therapy, patients will be followed every 6 months for overall survival only and for serious, unexpected and related adverse events (as per Section 11.1). A Short Follow-up Report should be completed.

Table 10: Schedule of Evaluation *After* Protocol Treatment for Patients Without Progressive Disease

Investigations		After Treatment
<b>Radiology</b> <i>To ensure comparability, the baseline exams/ scans and subsequent exams/ scans to assess response must be performed using identical techniques.</i>	<ul style="list-style-type: none"> <li>Skeletal survey (including skull, all long bones, pelvis and chest)</li> </ul>	As clinically indicated
	<ul style="list-style-type: none"> <li>Extra-medullary plasmacytomas should be assessed by CT, PET/CT scan or MRI</li> </ul>	Only required to confirm CR or better, or to confirm PD
<b>Other Investigations</b> Including disease assessment	<ul style="list-style-type: none"> <li>SPEP and immunofixation (<i>if required to confirm CR</i>)</li> <li>Serum Free Light Chain assay (sFLC)</li> <li>24-hour urine protein with urine protein electrophoresis (UPEP)* and urine immunofixation electrophoresis (UIFE)**</li> <li>Quantitative immunoglobulins</li> </ul>	Every 4 weeks***
<p>* 24 hour assessment, no substitute method is acceptable.</p> <p>** Only if UPEP <math>\geq</math> 200 mg/24 hours at baseline. Please note that UPEP and immunofixation is required to be completed to confirm VGPR (when serum and urine M-protein are not measurable), CR and sCR even if UPEP &lt; 200 mg/24 hours at baseline. See Table 11 of the protocol for more information.</p> <p>*** Patients who discontinue therapy due to toxicity in the absence of progression should be followed every <u>4 weeks until progression, or initiation of non-protocol therapy</u> for the first 3 months after end of treatment. Following 3 months after the end of treatment, patients can be followed every 3 months.</p>		

## 10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

### 10.1 Definitions

10.1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

10.1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

### 10.2 Response and Evaluation Endpoints

10.2.1 Response: Response and progression will be evaluated in this study using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) as summarized in Table 11 below:

Table 11: Response According to International Myeloma Working Group Uniform Response Criteria

Response Subcategory <sup>a</sup>	Multiple Myeloma Response Criteria
Stringent Complete Response <sup>b,c</sup> (sCR)	<ul style="list-style-type: none"> <li>• CR as defined below and</li> <li>• Negative immunofixation on the serum and urine and</li> <li>• Disappearance of any soft tissue plasmacytomas <sup>d</sup> and</li> <li>• &lt; 5% plasma cells in bone marrow biopsy and</li> <li>• Normal SFLC ratio and</li> <li>• Absence of clonal cells in bone marrow <sup>d</sup> by immunohistochemistry or immunofluorescence. <sup>d</sup></li> </ul>
Complete Response <sup>b,c</sup> (CR)	<ul style="list-style-type: none"> <li>• Negative immunofixation on the serum and urine and</li> <li>• Disappearance of any soft tissue plasmacytomas <sup>d</sup> and</li> <li>• &lt; 5% plasma cells in bone marrow biopsy.</li> </ul>
Very Good Partial Response <sup>b</sup> (VGPR)	<ul style="list-style-type: none"> <li>• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or</li> <li>• ≥90% reduction in serum M-protein with urine M-protein level &lt;100 mg/24 hours</li> <li>• If the serum and urine M-protein are not measurable, a ≥90% decrease in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria. However, documentation of VGPR requires collection and analysis of 24 hour urine sample for UPEP and immunofixation and confirmation to be negative.</li> <li>• If present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.</li> </ul>
Partial Response <sup>b</sup> (PR)	<ul style="list-style-type: none"> <li>• ≥50% reduction in serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to &lt;200 mg/24 hours</li> <li>• If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria.</li> <li>• If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein provided baseline bone marrow percentage was ≥30%</li> <li>• If present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.</li> </ul>

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Table 11 continued:

Response Subcategory <sup>a</sup>	Multiple Myeloma Response Criteria
Minimal response (MR)	<ul style="list-style-type: none"> <li>• 25-49% reduction in serum M-protein, and 50-89% reduction in 24-hour urinary M-protein, if <math>\geq 200</math> mg/24 hours at baseline</li> <li>• If the serum and urine M-protein are not measurable, a decrease of 25-49% in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria</li> <li>• If present at baseline, a <math>\geq 50\%</math> reduction in the size of soft tissue plasmacytomas is also required.</li> </ul>
No change Stable disease <sup>b</sup>	<ul style="list-style-type: none"> <li>• Not meeting the criteria for CR, VGPR, PR or progressive disease</li> </ul>
Progressive Disease <sup>c</sup> (PD)	<p>Any one or more of the following:</p> <ul style="list-style-type: none"> <li>• Increase of <math>\geq 25\%</math> from lowest response value in: <ul style="list-style-type: none"> <li>– Serum M-component and/or (the absolute increase must be <math>\geq 0.5</math> g/dL (5 g/L))</li> <li>– Urine M-component and/or (the absolute increase must be <math>\geq 200</math> mg/24 h)</li> <li>– Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be <math>&gt;10</math> mg/dL (0.1g/L) <sup>f</sup></li> <li>– Bone marrow plasma cell percentages(absolute percentage must be <math>\geq 10\%</math>)</li> </ul> </li> <li>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas <sup>g,h,i</sup></li> <li>• Development of hypercalcemia (corrected serum calcium <math>&gt; 11.5</math> mg/dL (0.115 g/L) or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.</li> </ul>

Note: Source: [Durie 2006; Rajkumar 2011] (modified for protocol purposes).  
FLC = serum light chain;

Note: Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. For patients without measurable protein on UPEP at baseline, UPEP will need to be repeated to confirm a response.

For IgA myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage changes applies as for serum M-protein.

a Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter.

b **All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments** made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of  $\geq 6$  weeks.

c Date of sCR or CR should be **the earliest date** all applicable blood and urine parameters are met, which is subsequently confirmed by bone marrow

d Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of  $> 4:1$  or  $< 1:2$ .

e **Determination of PD while on study requires 2 consecutive assessments** made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of  $\geq 1$  g/dL (10 g/L) from nadir are sufficient to define progression if nadir M-component is  $\geq 5$  g/dL (50 g/dL).

f Free light chain (sFLC) escape is not part of IWMG response criteria used in this study but please note that we will be tracking sFLC escapes separately

g Plasmacytomas: A definite increase in the size is defined as a  $\geq 50\%$  increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm<sup>2</sup>. Plasmacytomas of lesser size will

be considered non-measurable.

- h The requirement for bi-directional measurements applies only to plasmacytomas.
- i The plasmacytoma specifications for PD are based on Amgen's interpretation of the IMWG-URC and practical considerations for study execution.

### 10.3 Survival Endpoints

#### 10.3.1 Progression Free Survival

PFS is the time from start of the study treatment to disease progression, death or last follow-up.

#### 10.3.2 Overall Survival

OS is the time from the start of study treatment to death or last follow-up.

### 10.4 Methods of Measurement

- 10.4.1 Disease response and progression assessments include (but are not limited to): SPEP, UPEP, immunofixation, SFLC, bone marrow sample evaluation, serum calcium, plasmacytoma evaluation, and skeletal survey. Multiple myeloma assessment should be based on calendar day, regardless of cycle delay.

#### Extramedullary Plasmacytoma Assessment

- A plasmacytoma evaluation will be conducted at baseline only if a lesion is suspected clinically. Historical assessment for extramedullary plasmacytoma evaluation done as part of standard of care may be used as baseline as long as it was performed within 30 days prior to cycle 1 day 1 dosing.
- Measurable lesions must have a longest diameter of at least 1 cm and the product of cross diameter is at least 1 cm<sup>2</sup>. Plasmacytomas of lesser size are considered unmeasurable. Bidimensional lesion measurements must be performed and recorded in the designated eCRF. The same technique may include: palpation, ultrasound, x-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), or other standard-of-care method must be employed for each measurement.

#### Skeletal Survey

- Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri.



## 11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all “reportable” serious adverse events are subject to expedited reporting using the CRO SAE form. The term ‘reportable SAE’ is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CRO.

### 11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events that are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those that are not consistent in either nature or severity with information contained in the Investigator’s Brochure.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

In addition, because cases of hepatic failure, including fatal cases, have been reported in patients taking carfilzomib, as a precaution, the following will be reported in an expedited manner in this study:

- ALT or AST  $\geq 3$  times the institutional upper limit of normal

### 11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CRO Generic Data Management Guidebook for EDC Studies posted on the MYX.1 of the CRO website ([www.ctg.queensu.ca](http://www.ctg.queensu.ca)).

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Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to the CRO via EDC system.

Within 10 days: Update Serious Adverse Event Report as much as possible and submit report to the CRO via EDC system.

*EDC SAE web application interruption:*

In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

Max Sherry, MYX.1 Study Coordinator  
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to the CRO on the paper SAE Report must also be entered by the site into the EDC SAE web application.

*Local internet interruption:*

If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the MYX.1 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to as indicated above. Once internet connectivity is restored, the information that was FAXED to the CRO on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CRO Safety Desk for further instructions (613-533-6430).

### 11.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

#### 11.3.1 Pregnancy Prevention

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 5.1.7. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

#### 11.3.2 Pregnancy Reporting

The investigator is required to report to CRO any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the completion of cyclophosphamide treatment must be reported, as well as pregnancies that occur up to 30 days after completion of carfilzomib for female participants, and 90 days for female partners of male participants.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CRO Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CRO in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CRO.

Documents outlined above (including updates) must be sent to the CRO safety desk (613-533-2812/[safety-desk@ctg.queensu.ca](mailto:safety-desk@ctg.queensu.ca)).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

#### 11.3.3 Exposure Reporting

The investigator is required to report to CRO any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. In addition, an exposure includes an infant consuming breast milk produced by either a participant, or a non-study participant who swallowed study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure using the CRO Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual. All follow-up reports must be submitted to CRO in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CRO.

Documents outlined above (including updates) must be sent to the CRO safety desk (613-533-2812/[safety-desk@ctg.queensu.ca](mailto:safety-desk@ctg.queensu.ca)).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

#### 11.4 CRO Responsibility for Reporting Serious Adverse Events to Health Canada

The CRO will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (SUSARs) (or for which a causal relationship with protocol treatment cannot be ruled out).

11.5 CRO Reporting Responsibility to AMGEN

AMGEN will be notified (using CIOMS) of all regulatory reportable serious adverse events (SUSARs) within 24 hours of submitting the report to Health Canada.

Note: “Death, cause unknown” will be processed as a SUSAR.

Pregnancies and lactation exposures reports will be provided to AMGEN within 10 days of becoming aware of the event. AMGEN will be notified (using CIOMS) of SUSARs resulting from pregnancy or lactation exposure within 24 hours of submitting the report to Health Canada.

11.6 AMGEN Reporting Responsibility

Amgen will report safety updates from non-CRO trials (Safety Updates) for carfilzomib to Health Canada in accordance with applicable guidelines and regulations. Amgen will provide to CRO updated IBs and Unanticipated Problems (safety information) which result in a change to the protocol or consent will be sent within 7-15 days.

11.7 Reporting Safety Reports to Investigators

CRO will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CRO. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the MYX.1 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CRO trial MYX.1 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CRO can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

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## 12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

### 12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness that would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Tumour progression or disease recurrence as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

### 12.2 Therapy After Protocol Treatment is Stopped

(see Section 10.0 for response definition)

- For all responding patients (SD or better) therapy will continue as per protocol until progression, intolerance or death.
- Patients who progress (treatment failure) will go off study at the time progression is documented clinically, biochemically and/or radiographically.

Therapy after protocol treatment is stopped is at the discretion of the investigator.

Patients who have received any protocol treatment should be followed for progression free and overall survival as per Section 9.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

There will be no central radiology review for this study

13.2 Central Pathology Review

There will be no central pathology review for this study.

## 14.0 STATISTICAL CONSIDERATIONS

### 14.1 Objectives and Design

This is a phase II single arm study assessing the response rate of CCD regimen after 4 cycles of treatment.

### 14.2 Primary Endpoints and Analysis

The response rate observed in the historical comparator (CyBorD) in this patient population is around 65%, and we expect achieve a 15% increase with the study treatment to attain an 80% ORR (PR or better) after 4 cycles.

### 14.3 Secondary Endpoints

- To determine the safety and toxicity profile of the combination.
- To determine the depth of response including rates of sCR, CR, VGPR, PR by current IMWG criteria.
- To determine progression-free survival.
- To determine the 2-year overall survival.

Both the overall survival (OS) and progression free survival (PFS) are secondary but very important endpoints of this study. After the final analysis for 4 cycle response rate is performed, all patients will continue to be followed for an additional 1 year to have robust data for both OS and PFS analyses. Follow up will continue for a maximum of 36 months after the last accrual, or until all patients have discontinued protocol therapy, whichever is sooner.

### 14.4 Exploratory Endpoints

- To perform a descriptive cost analysis of CCD therapy in relapsed and refractory multiple myeloma.

A descriptive analysis of costs associated with weekly carfilzomib, cyclophosphamide and dexamethasone treatment will be performed, from the perspective of the Canadian health care system. Resource utilization for each patient will be determined from submitted electronic case report form data. Unit costs will be obtained from provincial / national databases and assumed to be representative of costs across the country. A mean treatment cost per cycle will be derived, and a range of costs for each patient over the course of their participation in the study calculated. Costs will be expressed in Canadian dollars, adjusted to the year of study completion / analysis.

### 14.5 Sample Size

Assume  $H_0: p=0.65$  and  $H_A: p=0.80$ , the planned sample size is 69 evaluable patients to achieve a 79.5% power. The two sided type I error was set at 0.05. CCD combination will be considered clinically valuable if 53 or more patients achieve PR or better after 4 cycles of treatment. Accounting for 5-10% non-evaluable patients, the total number of patients to be enrolled will be 73 – 76. The sample size was calculated based on one proportion Clopper-Pearson Binomial exact method.

### 14.6 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.



## 15.0 PUBLICATION POLICY

### 15.1 Authorship of Papers, Meeting Abstracts, Etc.

- 15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:
- The first author will generally be the chair of the study.
  - A limited number of the members of the Myeloma Canada Research Network may be credited as authors depending upon their level of involvement in the study.
  - Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

#### Dissemination of Trial Results

MCRN will inform participating investigators of the primary publication of this trial.

### 15.2 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by MCRN, Amgen and the academic CRO Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

## 16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

### 16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

### 16.2 Inclusivity in Research

CRO does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CRO that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CRO clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CRO policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CRO studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CRO will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

### 16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CRO trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CRO may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CRO recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CRO requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CRO may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CRO allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial. In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

#### 16.3.1 Obtaining Consent for Pregnancy/Exposure Reporting

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CRO.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/*exposure*. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

#### Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an “Exposure Follow-up” consent form (even if they are a participant in the main study) prior to collecting information about the child.

#### 16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CRO all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CRO will provide this information to centres as well.

If this trial is discontinued at anytime by the centre (prior to closure of the trial by the CRO), it is the responsibility of the qualified investigator to notify the CRO of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CRO or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

#### 16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CRO that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CRO will inform the investigator/institution as to when the essential documents no longer need to be retained.

#### 16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

#### 16.7 On-Site Monitoring/Auditing

Site monitoring/auditing will be conducted at participating centres by the CRO in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

The CRO has reserved the right to audit participating centres.

Audits may only be conducted after consultation with CRO.

#### 16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the “Registration/Randomization and Data Management Guidebook” posted on the MYX.1 area of the study web-site [www.ctg.queensu.ca](http://www.ctg.queensu.ca).

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AMEND #1: 2017-JAN-31; AMEND #2: 2017-OCT-11

APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (within 21 days of registration)	During Protocol Treatment			After Completion of Protocol Therapy	
		Day 1 of Cycle 1, 2, and 3	Day 15 of Cycle 1 and 2	Day 1 of each cycle starting with cycle 4	Every 4 weeks after end of therapy until Progressive Disease €	Every 6 months after disease progression
Physical						
Medical History <sup>1</sup>	X					
Physical exam, including neurological and plasmacytoma assessment <sup>2</sup> ( <i>if appropriate</i> )	X	X		X		
Weight, BSA	X	X		X		
Height, Vital Signs	X					
Performance Status	X	X		X		
Survival and SAEs <sup>3</sup>	X	X	X	X	X	X
Hematology*						
Complete blood count with differential	X	X <sup>4</sup>	X	X		
Biochemistry*						
Full serum chemistry panel <sup>5</sup>	X	X <sup>4</sup>				
Abbreviated serum chemistry panel I <sup>5</sup>			X			
Abbreviated serum chemistry panel II <sup>5</sup>				X		
Radiology						
Skeletal Survey**	X (within 30 days)					
CT, PET CT or MRI	X <sup>2</sup> (within 30 days)					
Other Investigations						
Beta2-microglobulin	X					
Serum protein electrophoresis (SPEP) with immunofixation	X	X		X	X	
24h Urine protein with urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE) <sup>#</sup>	X	X		X	X	
Urinalysis including macroscopic examination (specific gravity, protein, pH, glucose, ketones, blood, leukocyte esterase and nitrite)	X					
Urinalysis with microscopic examination (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast)	X					
Serum free light chain assay (sFLC)	X	X		X	X	
Quantitative serum immunoglobulins	X	X		X	X	
Bone Marrow Assessment***	X (within 8 weeks prior)					
Cytogenetic assessment of marrow plasma cells by FISH	X (within 8 weeks prior)					
12-lead ECG with QTC interval	X					
Serum Pregnancy Test ( <i>For women of childbearing potential only</i> )	X (within 72 hours)	X		X		
Adverse Events						
Adverse Event Assessment	X	X	X	X	X <sup>##</sup>	

footnotes on next page ...



1	Please refer to Table 6.0 for more information.
2	Only required if plasmacytomas are being followed. Plasmacytoma assessment required to confirm CR or better, or to confirm PD.
3	Serious, unexpected and related adverse events (as per Section 11.1).
4	Not required at Day 1, Cycle 1 if blood work at screening was completed within 7 days of D1C1.
5	Please refer to Table 6.0 and 9.0 for the full list of investigations required for biochemistry.
*	Bloodwork Timing: <u>Pre-treatment blood draws</u> may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do <u>interim blood draws</u> within 24 hours of the day specified in the protocol.
**	Required within 30 days prior to registration and as clinically indicated throughout study.
***	Required at screening to assess clonal disease burden with subsequent marrows only required to confirm CR if achieved by biochemical parameters.
#	Only if UPEP $\geq$ 200 mg/24 hours at baseline. Please note that UPEP and immunofixation is required to be completed to confirm VGPR (when serum and urine M-protein are not measurable), CR and sCR even if UPEP $<$ 200 mg/24 hours at baseline. See Table 11 of the protocol for more information.
##	Required at the 4 week post treatment visit only.
€	Patients who discontinue therapy due to toxicity in the absence of progression should be followed every <u>4 weeks until progression, or initiation of non-protocol therapy</u> for the first 3 months after end of treatment. Following 3 months after the end of treatment, patients can be followed every 3 months.

## APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA					
Karnofsky and Lansky performance scores are intended to be multiples of 10.					
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.
* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.					

### APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

#### General

Carfilzomib will be supplied by Amgen.

Cyclophosphamide and dexamethasone for this protocol are commercially available and sourced from the Canadian market.

#### Distribution

Drug distribution will be managed through an Interactive response technology system called Endpoint. Please refer to the MYX.1 trial specific website for more information/instructions on carfilzomib ordering and distribution.

#### Drug Accountability

It is the responsibility of each site to maintain drug accountability logs for carfilzomib.

#### APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the “CRO EDC Generic Data Management Guidebook” posted on the MYX.1 area of the study web-site [www.ctg.queensu.ca](http://www.ctg.queensu.ca).

The electronic CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required*
Eligibility Checklist		At the time of registration	Copies of the signed Consent form**, relevant pathology and radiology reports (including bone marrow aspirate, biopsy and cytogenetics), serum protein electrophoresis, serum free light chains, quantitative immunoglobulins, 24 hour urine protein electrophoresis reports)
Baseline Report		Within 2 weeks of registration	
Treatment Report	Every 4 weeks (28 days) after each cycle	Within 2 weeks of the end of each cycle	Bone marrow (if applicable), serum protein electrophoresis, serum free light chains, quantitative immunoglobulins, 24 hour urine protein electrophoresis and relevant radiology reports
Concomitant Medication Report	Continuous running-log folder		
End of Treatment Report	When the patient goes off protocol treatment	Within 2 weeks of the end of treatment	
Post Treatment Report	To be completed once on all patients, 4 weeks after going off protocol treatment	Due within 2 weeks after contact with patient	Bone marrow (if applicable), serum protein electrophoresis, serum free light chains, quantitative immunoglobulins, 24 hour urine protein electrophoresis and relevant radiology reports
Follow-up Report	Every 4 weeks <u>until</u> progression (following 4 week Post Treatment Report) €	Within 2 weeks of follow - up visit	Bone marrow (if applicable), serum protein electrophoresis, serum free light chains, quantitative immunoglobulins, 24 hour urine protein electrophoresis and relevant radiology reports

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Relapse/Progression Report	Upon disease progression	Within 4 week of confirmation	Relevant radiology, operative and pathology reports. Bone marrow (if applicable), serum protein electrophoresis, serum free light chains, quantitative immunoglobulins, and 24 hour urine protein electrophoresis reports
Short Follow-up Report	Every 6 months after progression	Within 2 weeks follow-up visit	
Death Report	When patient dies	Within 2 weeks of patient's death	Autopsy/post-mortem report, if done
SAE Report***	At the time of the event	See Section 11	Any relevant reports as requested
<p>* Supporting Documentation should be uploaded into the EDC system.</p> <p>** It is acceptable to submit only the signature page(s) of the main consent provided that the version date of the consent form is indicated.</p> <p>*** See Section 11.0 Serious Adverse Event Reporting for details.</p> <p>€ Patients who discontinue therapy due to toxicity in the absence of progression should be followed every <u>4 weeks until progression, or initiation of non-protocol therapy</u> for the first 3 months after end of treatment. Following 3 months after the end of treatment, patients can be followed every 3 months.</p>			

## APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)).

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to registration.	Amanda Bontje Clinical Trials Assistant Email: <a href="mailto:abontje@ctg.queensu.ca">abontje@ctg.queensu.ca</a>	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on Trial Website: <a href="http://www.ctg.queensu.ca">http://www.ctg.queensu.ca</a> under: <i>Clinical Trials</i>		
PRIMARY CONTACTS FOR GENERAL PROTOCOL- RELATED QUERIES (including eligibility questions and protocol management)	Max Sherry Study Coordinator Email: <a href="mailto:msherry@ctg.queensu.ca">msherry@ctg.queensu.ca</a>	613-533-6430	613-533-2941
	or: Dr. Annette Hay Senior Investigator Email: <a href="mailto:ahay@ctg.queensu.ca">ahay@ctg.queensu.ca</a>	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Christopher Venner Study Chair Email: <a href="mailto:christopherpaul.venner@albertahealthservices.ca">christopherpaul.venner@albertahealthservi ces.ca</a>	780-432-8757	780-432-8888
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Annette Hay Senior Investigator or: Max Sherry Study Coordinator	613-533-6430	613-533-2941
DRUG ORDERING	See Appendix III and trial website for full details and contact information.		